DETAILED ACTION

Status of Claims

1. Applicants' response, filed 4/29/2011, to the Office Action mailed 12/30/2010 is acknowledged. Applicants submitted amendments to the Specification, Claims and the Drawings for Figure 1, and presented arguments in response to the Office Action.

2. Claims 1-25 are pending.

3. Claims 1, 2, 7, 8, 10-13, 18, 19, 21, 22, 24 and 25 are presently under consideration.

4. Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Drawings

5. The drawings are objected to because the quality of Fig. 1 is such that it cannot be clearly read and interpreted. The replacement drawings, filed 4/29/2011, did not overcome this objection. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If

a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

6. Claims 21 and 22 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 1 and 2 are drawn methods requiring the administration a compound of formula I or a pharmaceutically acceptable salt thereof. Claims 21 and 22 are drawn a method of claims 1 and 2, respectively, comprising administering a compound of formula I or a pharmaceutically acceptable salt thereof; this is not further limiting of Claims 1 and 2.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 7, 8, 10-12, 18, 21, 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement rejection.

To be enabling, the Specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996). (As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation")

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833,839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to a method of inhibiting hyperproliferative cell growth in a patient in need thereof, comprising administering to said patient an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicants' invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving

unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ 2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112, 1st Paragraph is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). To that extent, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See *Chiron Corp v. Genetech, Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching. The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology."

Hyperproliferative cell growth encompasses many conditions, such as, neoplasms, hyperplasias, and benign or malignant tumors (e.g., cancers). When just considering hyperplasias, one skilled in the art would recognize many different types of hyperplasias. Hyperplasia, which is an abnormal increase in the number of cells in a tissue or organ, includes congenital adrenal hyperplasia, benign prostatic hyperplasia, C-cell hyperplasia, adrenocortical hyperplasia, cutaneous lymphoid hyperplasia, fibrous inflammatory hyperplasia, G cell hyperplasia, hepatic hyperplasia, lipoid hyperplasia, neoplastic hyperplasia, squamous hyperplasia, and verrucous hyperplasia, to name a few. See Dorland's Illustrated Medical Dictionary, 31st Edition ("Hyperplasia", Saunders Elsevier, 2007, pp. 906-907; previously cited).

2. The breadth of the claims

The invention relates to methods of inhibiting hyperproliferative cell growth in a patient, encompassing a plethora of diverse diseases (*supra*), comprising administering a compound of formula (I) (recited in Claim 1). The claimed compounds encompass a multitude (thousands) of different compounds having chemically distinct substituents. Dependent Claim 12 recites three of which read on formula (I) (Compounds 73, 276 and 285). Claim 18 limits the compounds of Claim 1 to those having a ClogP value of ≤ 5, a molecular weight of ≤ 500 Daltons, and ≤ 10 hydrogen bond donors and acceptors. Dependent Claims 7, 8 and 10 limit the patient population to those suffering from a neoplasm or hyperplasia (Claim 7); a benign or malignant tumor (Claim 8); or leukemia, lymphoma, ovarian cancer and breast cancer (Claim 10). New Claims 24 and 25, which depend from Claim 1, are drawn to compounds 27 and 276, respectively.

Whether any particular compounds encompassed by the claims would have any activity *in vitro*, let alone *in vivo*, would require synthesis and purification of the compound followed by testing in an *in vitro* or *in vivo* assay. Predicting, *a priori*, whether a given compound will inhibit hyperproliferative cell growth does not appear to be possible.

3. The amount of direction or guidance provided and the presence or absence of working examples

The Specification discloses, at page 138, that "[h]yperproliferative cell disorders include, *e.g.*, cancers, blood vessel proliferative disorders, fibrotic disorders, and autoimmune disorders." Page 136 of the Specification states "It is proposed that compounds of the invention, by interacting with $p56^{lck}$, particularly with an SH2 domain thereof, modulate the kinase activity of the protein and/or modulate its ability to interact with a corresponding cellular binding protein, and thereby modulate immune responses, directly or indirectly, and neoplastic cell proliferation." The Specification discloses that 2 compounds of formula (I) (compounds 73 and 276) were tested in an *in vitro* assay for the inhibition of "p56 Lck SH2 domain association with phosphotyrosine-containing C-terminal ITAM2 peptide." According to the Specification, immunoblots from the assays (Figure 1-A) show compound 276 has "significant inhibitory activities at 100 μM [and] Figure 1 (panel B) shows a dose dependent inhibition of co-precipitation by the inhibitor 73; at 40 μM (lane 5) the compound significantly blocked p56 Lck association with the ITAM2 peptide. The 34 preferred compounds identified herein were shown to have significant inhibitory activity at 100 μM....Of these, compounds 73 and 92 show strong

inhibitory activity at 40 and 10 μM, respectively." (Pages 149-152) It is noted by the Examiner that only 3 (compounds 73, 276 and 285) of the 34 disclosed compounds read on formula (I) and actual data is presented for only 2 of these compounds (73 and 276). Figure 2 of the disclosure present *in vitro* data for inhibition of ^{3}H-thymidine uptake in mixed lymphocyte culture. According to the Specification (page 152), 24 of the 34 identified compounds were tested, with 13 compounds showing inhibitory activity at 100 μM concentration (shown in Figure 2). It is disclosed that compound 73 was not tested at 100 μM because of solubility issues. It is noted that only 2 compounds (compounds 73 and 276) were presented as having activity. The Specification also discloses that 7 of the compounds showed "biphasic" activity, "where positive inhibitory activity is observed at higher concentration (100 μM) and negative inhibition (i.e. activation) occurs at lower concentrations (1 μM)."

There are no data presented, either *in vitro* or *in vivo*, that show the inhibition of any form of hyperproliferative cell growth.

At page 136 of the Specification, it is disclosed that "[a]ll compounds can be prepared fully conventionally, using known reaction chemistry, starting from known materials or materials conventionally preparable....Most compounds of the invention are readily available from standard sources, such as chemical supply houses, or can be generated from commercially available compounds by routine modifications. All tested compounds were purchased from commercial vendors and all compounds specifically described in the application are known compounds." The disclosure does not provide

any exemplary synthetic pathways for the claimed compounds, nor does it provide actually sources of the compounds.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used to inhibit all (or any) types of hyperproliferative cell growth encompassed by the claims.

Genentech Inc. vs. Nova Nordisk states, "**[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable**" (42 USPQ 2d 1001, Fed. Circuit 1997).

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no reasonable assurance of success.

9. Claims 2, 13, 19 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the Specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement rejection.

To be enabling, the Specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996). (As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation")

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833,839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to a method of inhibiting the binding of a $p56^{lck}$ molecule via an SH2 domain thereof to a corresponding cellular binding protein, or inhibiting the activity of a $p56^{lck}$ comprising administering a compound of formula I or a pharmaceutically acceptable salt thereof.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicants' invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how

different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ 2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112, 1st Paragraph is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). To that extent, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See *Chiron Corp v. Genetech, Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching. The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology."

2. The breadth of the claims

The claims are drawn to inhibiting the binding or activity of a $p56^{lck}$ molecule, comprising administering a compound of formula I or a pharmaceutically acceptable salt. The claimed compounds encompass a multitude (thousands) of different

compounds having chemically distinct substituents. Dependent Claim 13 recites three compounds which read on formula (I) (Compounds 73, 276 and 285). Claim 19 limits the compounds of Claim 2 to those having a ClogP value of ≤ 5, a molecular weight of ≤ 500 Daltons, and ≤ 10 hydrogen bond donors and acceptors. A target for administration of the compounds is not claimed.

Whether any particular compounds encompassed by the claims would have any activity *in vitro* or *in vivo*, would require synthesis and purification of the compound followed by testing in an *in vitro* or *in vivo* assay. Predicting, *a priori*, whether a given compound would modulate the binding or activity of a $p56^{lck}$ molecule does not appear to be possible.

3. The amount of direction or guidance provided and the presence or absence of working examples

Page 136 of the Specification states "It is proposed that compounds of the invention, by interacting with $p56^{lck}$, particularly with an SH2 domain thereof, modulate the kinase activity of the protein and/or modulate its ability to interact with a corresponding cellular binding protein, and thereby modulate immune responses, directly or indirectly, and neoplastic cell proliferation." The Specification discloses that 2 compounds of formula (I) (compounds 73 and 276) were tested in an *in vitro* assay for the inhibition of "p56 Lck SH2 domain association with phosphotyrosine-containing C-terminal ITAM2 peptide." According to the Specification, immunoblots from the assays (Figure 1-A) show compound 276 has "significant inhibitory activities at 100 μM [and] Figure 1 (panel B) shows a dose dependent inhibition of co-precipitation by the inhibitor

73; at 40 μM (lane 5) the compound significantly blocked p56 Lck association with the ITAM2 peptide. The 34 preferred compound identified herein were shown to have significant inhibitory activity at 100 μM....Of these, compounds 73 and 92 show strong inhibitory activity at 40 and 10 μM, respectively." (Pages 149-152) It is noted by the Examiner that only 3 (compounds 73, 276 and 285) of the 34 disclosed compounds read on formula (I) and actual data is presented for only 2 of these compounds (73 and 276). Figure 2 of the disclosure present *in vitro* data for inhibition of ^{3}H-thymidine uptake in mixed lymphocyte culture. According to the Specification (page 152), 24 of the 34 identified compounds were tested, with 13 compounds showing inhibitory activity at 100 μM concentration (shown in Figure 2). It is disclosed that compound 73 was not tested at 100 μM because of solubility issues. It is noted that only 2 compounds (compounds 73 and 276) were presented as having activity. The Specification also discloses that 7 of the compounds showed "biphasic" activity, "where positive inhibitory activity is observed at higher concentration (100 μM) and negative inhibition (i.e. activation) occurs at lower concentrations (1 μM)."

At page 136 of the Specification, it is disclosed that "[a]ll compounds can be prepared fully conventionally, using known reaction chemistry, starting from known materials or materials conventionally preparable....Most compounds of the invention are readily available from standard sources, such as chemical supply houses, or can be generated from commercially available compounds by routine modifications. All tested compounds were purchased from commercial vendors and all compounds specifically described in the application are known compounds." **The disclosure does not**

provide any exemplary synthetic pathways for the claimed compounds, nor does it provide actually sources of the compounds.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*), the absence of experimental evidence commensurate in scope with the claims, and the absence of any specific teaching on the synthesis or commercial source of the genus of compounds encompassed by formula I, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used to "inhibit the binding of a $p56^{lck}$ molecule via an SH2 domain thereof to a corresponding cellular binding protein, or inhibiting the activity of a $p56^{lck}$ molecule via an SH2 domain thereof."

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no reasonable assurance of success.

Response to Arguments

10. Applicants argue "amended claims 1 and 2 are commensurate in scope with the experimental examples provided in the specification that show inhibiting activities in the cellular functional assay. The exemplary guidance provided in the specification shows these compounds' inhibitive effect on hyperproliferative cell growth and $p56^{lck}$ activity. Since the specification discloses at least one method of using compounds 73 and 276, both of which bear a reasonable correlation to the entire scope of amended claims, a skilled artisan would not be burdened with undue experimentation to practice the claimed methods with the experimental guidance provided in the specification."

The Examiner respectfully disagrees. As discussed, *supra*, the Specification ***proposes*** "that compounds of the invention, by interacting with $p56^{lck}$, particularly with an SH2 domain thereof, modulate the kinase activity of the protein and/or modulate its ability to interact with a corresponding cellular binding protein, and thereby modulate immune responses, directly or indirectly, and **neoplastic** cell proliferation (emphasis added)." There are no data or any other form of support that the claimed compounds actually have any inhibitory effect on any hyperproliferative cell growth, either *in vitro* or *in vivo*. The Specification shows that some of the compounds had "biphasic" activity, "where positive inhibitory activity is observed at higher concentration (100 μM) and negative inhibition (i.e. activation) occurs at lower concentrations (1 μM)"; thus demonstrating further unpredictability of the instant invention. Furthermore, the Specification does not teach any synthetic pathway(s) or commercial source(s) for the instantly claimed genus of compounds.

Therefore, a skilled artisan **would** be burdened with undue experimentation to practice the claimed methods.

Conclusion

11. Claims 1, 2, 7, 8, 10-13, 18, 19, 21, 22, 24 and 25 are rejected.

12. No claims are allowed.

13. Applicants' amendments necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GREGG POLANSKY whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571) 272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1629

/James D Anderson/
Primary Examiner, Art Unit 1629